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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/319,736	08/02/1999	ELISABETH WOLPERT	000500-182	3510

21839 7590 05/03/2006

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 05/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/319,736	WOLPERT ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *143-164* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *143-164* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 148, 155, 157, 160 and 161 have been amended. Claims 163 and 164 are added. Claims 143-164 are pending and under consideration.

The rejection of claims 155-157, 160 and 161 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record. Claim 164 is also rejected for the same reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 157 is drawn to a composition comprising cells isolated according to the method of claim 148. Claim 160 is drawn to cells isolated according to the method of claim 148, antigens or epitopes expressed by said cells. Claim 161 is drawn to a composition comprising immunological effector cells isolated according to the method of claim 155 and claim 164 is drawn to a composition comprising effector cells isolated by the method of claim 163. It is noted that claims 157 and 160 are dependent upon the cell isolated by the method of claim 148; the methods of claims 155 and 156 depend on the cells isolated by the method of claim 148, and that claim 161 is a method reliant on the identity of cell isolated by the method of claim 155, which in turn is reliant on claim 155 which is drawn to a process comprising stimulating isolated immunological effector cells in vitro with cell isolated according to the method of claim[s] 148. The products of claims 157, 160, 161 and 164 lack adequate written description, because the specification cannot adequately describe cells which have yet to be isolated. It logically follows that if a product itself is not adequately described, the method o f using said product cannot be adequately described.

Applicant argues that product-by-process claims are proper under USC 112, first paragraph. This has been considered but not found persuasive. The claims on which the instant compositions depend are drawn to a process of making a specific product because said method are reliant on screening for a particular "substance" ("treating cells with a substance") which would cause the effect of impairing cellular peptide processing for MHC presentation. without an adequate description of the genus of compounds encompassed by said "substance" the method

claims are screening methods for the substance, rather than process methods reliant on a specific substance. It is noted that the M.P.E.P.(2116) states

The materials on which a process is carried out must be accorded weight in determining the patentability of a process. Ex parte Leonard, 187 USPQ 122 (Bd. App. 1974). 2116.01 [R-2].

In the instant case, the method claims rely on a "substance" rather than a defined compound, therefore, in order to use the method claim it is necessary to screen for the particular characteristic which are required by the claim. Products which are isolated from said methods cannot be adequately described as they have not yet been subject to the screening method.

The rejection of claims 143-147, 159 and 162 are rejected under 35 U.S.C. 102(e) as being anticipated by Nair et al (U.S. 5,831,068) is maintained for reasons of record.

Claim 143 is drawn to a method of impairing cellular processing for MHC presentation comprising treating cells with a substance, wherein the substance is characterized in that tumor cells treated with the substance are subject to specific lysis by CTL encoded by endogenous MHC I dependent antigens of the TAP-deficient variant of said tumor cell which has been transfected with the stimulatory molecule, B7-1, thereby inducing immunological effector cells specific for endogenous epitopes associated with impaired cellular processing. Claim 144 embodies the method of claim 143 wherein the substance is selected for the group consisting of substances which inhibit the function of TAP, and substances which inhibit the expression of TAP. Claim 145 embodies the method of claim 143, wherein the substance is selected from the group consisting of ICP-47 of HSV type 1, IE12 of HSV, type 2, a gene encoding for a TAP inhibitor, a nucleotide sequence that I complementary to the polynucleotide encoding TAP, anti-sense oligonucleotides, and RNA destroying ribozymes. Claim 146 embodies the method of claim 143 wherein the substance inhibit the function and expression of the proteosome. Claim 147 embodies the method of claim 123, wherein the substance is selected from the group consisting of a peptide aldehyhde, Z-Leu, Leu, Lactacystin, DNA encoding a proteosome

inhibitor, a nucleotide sequence that is complementary to at least a part of the mRNA or DNA sequence encoding the proteosome, anti-sense and RNA-destroying ribozyme.

Claim 159 is drawn to a composition comprising a substance that impair peptide processing for MHC presentation and thereby induces immunological effector cell specific for endogenous epitopes associated with impaired cellular processing for MHC presentation, the substance being characterized in that tumor cells treated with the substance are subject to specific lysis by CTL elicited by endogenous MHC I dependent antigens of the TAP-deficient variant of said tumor cell which has been transfected with the stimulatory molecule B7.1; and a pharmaceutically acceptable adjuvant selected from cytokines, genes for cytokines, co-stimulatory molecules, gold beads and/or liposomes. Claim 162 is drawn to a kit comprising a substance that impairs cellular peptide processing for MHCV presentation, and thereby inducing immunological effector cells specific for endogenous epitopes associated with impaired cellular peptide processing for MHC presentation , the substance being characterized in that tumor cells treated with the substance are subject to specific lysis by CTL elicited by endogenous MHC I dependent antigens of the TAP-deficient variant of said tumor cell which has been transected with the stimulatory molecule B7-1; and cytokines, genes for cytokines, co-stimulatory molecules, gold beads and/or liposomes.

Nair et al teach a method of inhibiting MHC I pathway associated components in a cell which include cells deficient in a TAP protein activity or proteosome activity, prior to contacting said cell with an antigen (column 1, lines 60-64). Nair et al teach the introduction into a cell of a anti-sense oligonucleotide which is complementary to said MHC-pathway dependent protein, introduction into said cell of an RNA decoy which binds to an MHC I pathway associated protein, introduction of a ribozyme which specifically cleaves mRNA encoding an MHC I pathway associated protein into a cell, introduction of proteosome inhibitors such as lactacystin (column 2, lines 1-35). Nair et al teach cells comprising anti-sense inhibitors of TAP-2 (column 16, examples II and III), cells dendritic cells contacted with proteosome inhibitors (column 20, Example IX) which fulfills the specific embodiment of claims 153 and 154.
Nair et al disclose a composition comprising an anti-sense genetic construct including all or a portion of a gene encoding TAP-1 (column 8, lines 16-18) in combination with a lipid (column 8,

lines 38-41) thus fulfilling the specific embodiment of a substance that impairs cellular processing for MHC presentation as defined by claims 159 and 162, and a liposome.

Applicant argues that Nair fails to teach the presentation of "endgogenous" epitopes. this has been considered but not found persuasive. The "substance" disclosed by Nair [Nair et al disclose a composition comprising an anti-sense genetic construct including all or a portion of a gene encoding TAP-1 (column 8, lines 16-18) in combination with a lipid (column 8, lines 38-41) thus fulfilling the specific embodiment of a substance that impairs cellular processing for MHC presentation as defined by claims 159 and 162] would have the characteristic pf causing tumor cells treated with said substance to undergo specific lysis by CTL elicited by endogenous MHC I dependent antigens of the TAP-deficient variant of said tumor cell which has been transfected with the stimulatory molecule B7-1.

The rejection of claims 155-157, 160 and 161 under 35 U.S.C. 102(b) as being anticipated by Hammond et al (Nature, 1993, Vol. 364, pp. 158-161) s maintained for reasons of record. The specific embodiments of the claims are set forth above. Hammond et al disclose T2-A3 cells expressing wild-type env or gp120 protein and the clone A3.1, which lyzed said cells (page 158, second column, lines 19-26). It is noted that the recitation of limitations as regards the "substance" in claim 148 defines said substance, but does not confine the treated cells to tumor cells which have been transfected with B7-1. Hammond et al anticipate the instant claims because the M.P.E.P. (2113) states:

PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS.

Applicant again argues that Hammond fails to teach the presentation of endogenous antigens. However, as stated above, this has been considered but not found persuasive. The "substance" disclosed by Hammond et al fulfills the specific embodiment of a substance that impairs cellular processing for MHC presentation as defined by claims because said substance would have the characteristic pf causing tumor cells treated with said substance to undergo specific lysis by CTL elicited by endogenous MHC I dependent antigens of the TAP-deficient variant of said tumor cell which has been transfected with the stimulatory molecule B7-1.

The rejection of claims 155-157, 160 and 161 under 35 U.S.C. 102(a) as being anticipated by Wolpert et a (PNAS, Oct 1997, Vol. 94, pp. 11496-11501) is withdrawn in light of applicants foreign priority document.

The rejection of claims 148-158, 160 and 161 under 35 U.S.C. 103(a) as being unpatentable over Nair et al (U.S. 5,831,068) in view of Sanberg et al (Eur Journal of Immunology, 1996, Vol. 26, pp. 288-293) and Skipper et al (Journal of Experimental Medicine, 1996, Vol. 183, pp. 527-534) is maintained for reasons of record. New claims 163 and 164 are also rejected for the same reasons of record..

The specific embodiments of claims 155-157, 160 and 161 are recited above. Claim 163 embodies the method of claim 148 further comprising simulating the isolated effector cells in vitro with said isolated cells which activate CD+8 T lymphocytes that selective recognize cells showing endogenous epitopes associated with impaired cellular processing for MHC presentation and isolating immunological effector cells that selectively recognize cells having impaired cellular peptide processing for MHC presentation. Claim 164

Claim 148 is drawn to a process comprising treating cells in vitro with an effective dose of a substance that impairs cellular peptide processing for MHC presentation, wherein the substance is characterized in that tumor cells treated with the substance are subject to specific lysis by CTL elicited by endogenous MHC I dependent antigens of the TAP-deficient variant of said tumor cell which has been transected with the stimulatory molecule B7-1, and identifying cells which activate CD8 T lymphocytes that selectively recognize cells having endogenous epitopes associated with impaired cellular peptide processing foe MHC presentation. Claim 149 embodies the process of claim 148 wherein the substance inhibits the function and/or expression of TAP. Claim 150 embodies claim 149, wherein substance is selected from the group consisting of ICP-47 of HSV type 1, IE12 of HSV, type 2, a gene encoding for a TAP inhibitor, a nucleotide sequence that I complementary to the polynucleotide encoding TAP, anti-sense oligonucleotides, and RNA destroying ribozymes. Claim 151 embodies the method of claim 146, wherein the substance inhibit the function and expression of the proteosome. Claim 152 embodies the method of claim 151, wherein the substance is selected from the group consisting of a peptide aldehyhde, Z-Leu, Leu, Lactacystin, DNA encoding a proteosome inhibitor, a

nucleotide sequence that is complementary to at least a part of the mRNA or DNA sequence encoding the proteosome, anti-sense and RNA-destroying ribozyme. Claim 153 embodies the process of claim 148, wherein the cells are autologous cells/hematopoietic cells. Claim 154 embodies the method of claim 153 wherein the autologous and/or hematopoietic cells are dendritic cells, or cells form cancer tissues.

Claim 155 is drawn to a process comprising stimulating isolated immunological effector cells in vitro with cells isolated according the method of claims 148 and identifying immunological effector cells that selectively recognize cells showing impaired cellular peptide processing for MHC presentation. Claim 156 embodies the process of claim 155 wherein the immunological effector cells are CD8+ T lymphocytes.

Claim 157 is drawn to a composition comprising cells isolated according to the method of clam 148.

Claim 158 is drawn to a process comprising administering to a mammal immunological effector cells that selectively recognize cells showing impaired cellular peptide processing for MHC presentation.

Claim 160 is drawn to cells isolated according to the method of claim 148 or antigens or epitopes expressed by such cells and a pharmaceutically acceptable additive.

Claim 161 is drawn to a composition comprising immunological effector cells isolated according to the method of claim 155.

Nair et al teach methods of identifying cells which activate CD8+ lymphocytes in vitro (column 17, example IV and V) and methods comprising administering to a mammal CTL which recognize cells treated to eliminate a MHC I pathway associated protein. Nair et al do not teach endogenous epitopes associated with impaired cellular processing because Nair et al exposes said MHC I pathway deficient cells to exogenous peptides, therefore the immunological effector cells taught by Nair et al are not specific to the peptides associated with impaired cellular processing.

Sandberg et al teach that TAP1 deficient mice have a diverse CD8+ T cell repertoire that provides peptide-specific CTL (page 289-290, section 3.1 and page 290-291, section 3.3). Sanberg et al teach that these peptides are limited to those generated in the endoplasmic reticulum, such as those derived from signal sequences and those entering the ER independently of TAP (page 291, second column, lines 36-39 and page 292, first column, lines 1-2).

Skipper et al teach a peptide which is recognized by a CTL clone which recognizes the tyrosinase gene product on melanoma cells. Skipper et al teach that said peptide exhibits a posttranslational conversion of asparagine to aspartic acid. Skipper et al conclude that said post-translationally modified peptide is processed through the ER (abstract, last sentence). Skipper et al suggest that such post-translational changes can lead to the generation of new antigens which are relevant to tumor rejection (page 532, second column, lines 21-27).

It would have been prima facie obvious at the time the invention was made to carry out the methods of Nair et al without the subsequent step of pulsing the MHC I pathway deficient cells with exogenous peptides, and to use the resulting cells in a method of isolated specific CTL clones. One of skill in the art would have been motivated to do so by the teaching of Sanberg et al on the polyclonal nature of the T cell repertoire possible in TAP deficient transgenic mice, and the antigens derived from proteins via endoplasmic reticulum for presentation in a MHC I, TAP-independent mechanism, and by the teachings of Skipper et al on the possibility of new antigens afforded by proteins targeted to the ER by TAP independent mechanism, and the suggestion of Skipper et al that peptides derived from the ER, rather than the TAP pathway could represent a pool of new antigens important to tumor rejection.

Applicant argues that the teachings of Nair are entirely unrelated to the instant invention. this has been considered but not found persuasive. Nairs teachings are directly related to TAP as a mediator of antigen presentation by MHC I and the elimination of TAP which allows for the presentation of other antigens with are TAP-independent.

Applicant argues that Sandberg is concerned with a particular "question" However this is irrelevant to the facto of what is taught by Sandberg, i.e. that peptides which are modified in the ER can be presented by MHC I in a TAP-independent manner.

Applicant argues that Skipper et al "bears no discernable relationship to the presently claimed invention". This has been considered but not found persuasive. Applicant is referred to the rejection above which states that "Skipper et al conclude that said post-translationally modified peptide is processed through the ER (abstract, last sentence). Skipper et al suggest that such post-translational changes can lead to the generation of new antigens which are relevant to tumor rejection (page 532, second column, lines 21-27)".

Thus, it is obvious that the suppression or elimination of TAP processing can lead to the presentation of other antigens in a TAP-independent manner, which indeed is relevant to the instant invention. Further, it would have been obvious to isolate the immunological effector cells responding to the antigen-presenting cells exhibiting TAP-deficient processing in order to isolate effector cells which would recognize the TAP-independent antigens.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
4/30/2006